A CLINICOPATHOLOGICAL PROFILE OF PEDIATRIC LIVER TUMORS

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CERTIFICATE

This is to certify that this dissertation entitled **"A CLINICOPATHOLOGICAL PROFILE OF PEDIATRIC LIVER TUMORS"** is a bonafide work done by **Dr.E.MUTHUVEL**, in partial fulfillment of regulations of the TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY, Chennai.

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I declare that this dissertation entitled **"A CLINICOPATHOLOGICAL PROFILE OF PEDIATRIC LIVER TUMORS"** has been conducted by me under the guidance and supervision of **Prof.A.Senthamarai, M.D., DCP.** It is submitted in partial fulfillment of the requirements for the award of the M.D., Pathology, September 2006 examination to be held under Dr.M.G.R.Medical University, Chennai. This has not been submitted by me for the award of any degree or diploma from any other University.

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(E.MUTHUVEL)

CONTENTS

A CLINICO PATHOLOGICAL PROFILE OF PEDIATRIC LIVER TUMORS

INTRODUCTION

Primary liver tumors are the third largest group of solid abdominal neoplasms in children next to neuroblastoma and Wilms' tumor[28]. Hepatic tumors account for about 0.5% to 2% of all pediatric neoplasms[29]. Primary tumors of liver are divided into benign and malignant epithelial and non-epithelial neoplasms[18].

50 to 60% of primary liver tumors in children are malignant in which hepatoblastoma is most common followed by hepatocellular carcinoma[30]. Undifferentiated embryonal sarcoma of liver is the third most common malignant pediatric liver tumors[31]. In children, benign tumors constitute only 30% of liver tumors and most are hemangioendothelioma, followed by mesenchymal hamartoma[20]. Hepatocellular adenoma is a rare benign tumor in children[13].

Childhood liver tumors have received great attention because of their vast histologic variety, uncertainty about pathogenesis and classification and difficulties in treatment[1].

Benign tumors showed female preponderance when compared to malignant counterpart. Liver tumors are more common in the right lobe.

The availability of high quality ultrasonography, computerised axial tomography and magnetic resonance imaging have allowed us to characterise pediatric liver tumors with great precision using non invasive modalities.

REVIEW OF LITERATURE

HISTORICAL REVIEW

The term hepatoblastoma was proposed by Willis for all embryonal tumors containing hepatic epithelial parenchyma resembling more or less embryonal and fetal liver tissue[4].

Histological classification of hepatoblastoma was originally proposed by Willis and later modified by Ishak and Glunz[4].

In 1967 Ishak and Glunz refined the histopathologic criteria for hepatoblastoma. Since 1967 it has been generally known that hepatoblastoma arises in the liver of infants and young children, whereas patients older than five years of age tend to develop hepatocellular carcinoma. Ishak et al. have made a detailed comparative study of cases of hepatoblastoma and hepatocellular carcinoma[10].

Kasai and Watanabe classified hepatoblastoma into three histologic type (1) fetal (2) embryonal (3) anaplastic[7].

Ishak and Glunz, classified hepatoblastoma into two histological types (1) epithelial type (2) mesenchymal type (mixed hepatoblastoma)[7].

Gonzalez-Crussi has described three subtypes (1) fetal (2) embryonal (3) macrotrabecular[7].

According to kasai, the fetal type had a better prognosis than the embryonal type, whereas anaplastic tumors carried a constantly fatal prognosis[7].

Landing proposed that osteoid in mixed hepatoblastoma is an adventitious change, related to thrombotic phenomenon, as much as phlebolith form in venous angioma that thrombose and subsequently ossify[10].

Gonzalez and Mellissa disagree with this interpretation because contrary to the experience of Landing and of Denher, they were able to see extensive osteoid formation in pulmonary metastases of hepatoblastoma. Myogenic elements were not present in any of their cases, were not mentioned by Ishak and Gluntz and myogenic elements were absent in 70 cases studied by Kasai and Watanabe[10].

Regarding histopathology and prognosis, Ishak and Glunz reported no behavioural difference between epithelial and mixed hepatoblastoma in their review of 35 cases[4]. Lack, Neave and Vauter et al. suggested that tumors with a predominance of fetal histology may have more favourable prognosis[4].

Hepatic artery ligation for hemangioma was first reported by de Lovimier et al[9].

In 1970 steroid therapy applied for hemangioendothelioma by Touloukian's[9].

Undifferentiated embryonal sarcoma of the liver was a rare primary hepatic malignancy principally affecting patients of pediatric age. It is believed to be a primitive mesenchymal neoplasm which usually behaves in a highly malignant fashion[2].

Undifferentiated embryonal sarcoma of liver was recognised as a clinico pathological entity by Stocker and Ishak in 1978 on the basis of an Armed Forces Institute of Pathology series. Histogenesis of this tumor remains undetermined though the

possibility of it being a malignant counterpart of mesenchymal hamartoma was raised by Stanley and Ishak[25].

Lack, et al. reported only two cases of hepatic adenoma during 57 years at Children's Hospital, Boston[13].

Incidence

Primary hepatic neoplasms account for 0.5% to 2% of all pediatric neoplasms and comprise a variety of benign and malignant epithelial and mesodermal tumors. Of 716 cases of the 10 most commonly occurring hepatic neoplasms seen at the Armed Forces Institute of Pathology between 1970 and 1999. Hepatoblastoma, hepatocellular carcinoma and hemangioendothelioma accounted for almost 65%[23].

AGE

Gonzalez-Crussi studied 21 cases of hepatoblastoma at Children's Memorial Hospital of Chicago between 1954 and 1981, age range was between 37 hours to 12 years, seventeen cases were less than 2 years and three cases were neonates in first 3 months[10].

Ernest and Lack et al. reported 54 cases of hepatoblastoma in which age range was between 4 month - 4½ years with an average of 17 months[4].

Madhusudhana Murthy et al. reported 7 cases of hepatoblastoma in which age range was 5 months to 10 years, with an average of 25 months[15].

Gandhi et al. reported 6 cases of hepatoblastoma out of which age range was 8

months to 4 years, with an average of 19 months[8].

Jeng Chang Chen et al. studied 55 cases of hepatocellular carcinoma with age range of 4 to 16 years at diagnosis with median and mean age of 11 and 10.9 years respectively[11].

Yen-Hsuan Ni, studied 71 cases of hepatocellular carcinoma between 1964 to 1989 in which age range was 3 to 17 years, with an average of 9.7 years[30].

WeiJao Chen et al. studied 55 cases of hepatocellular carcinoma between 1976 to 1985 in which age range was 6 to 15 years. Two peaks in age presentation-first peak was between 7 to 9 years and second peak was 12 to 15 years[28].

Mistry et al. reported two cases of undifferentiated embryonal sarcoma in which both cases were 9 years old[17].

Lack et al. reported two cases of hepatocellular adenoma during 57 years at Children Hospital, Boston in which one case was in a new born and the other in a two year old child[13].

Francois et al. reported 16 cases of hemangioendothelioma in which age range was birth to 14 years and mean age was 2.3 years[6].

Georage et al. reported 16 infants with hemangioendothelioma in which mean age was 7 months and median age of 6 week and age range from 2 days to 14 years[9].

GENDER

Gonzalez Crussi et al. studied 21 cases of hepatoblastoma in which male, female ratio was 13:8[10].

Lack et al. studied 54 cases of hepatoblastoma and male, female ratio was nearly 2:1. (37 boys; 17 girls)[4].

Gandhi et al. reported 6 cases of hepatoblastoma, were with a male, female ratio was 5:1[8].

Khosla et al. reported 14 cases of primary malignant tumor, in which 12 cases of hepatoblastoma, with male, female ratio of 11:1 and two cases of embryonal sarcoma was reported with male, female ratio of 1:1[12].

Madhusundhana Murthy et al. reported 7 cases of hepatoblastoma and male, female ratio was 2.5:1[15].

Wei Jao Chen et al. studied 55 cases of hepatocellular carcinoma during 10 years period from 1976 to 1985 at National Taiwan University Hospital in Children <15 years, in which 34 were male and 10 females in M:F of 3.4:1 and 11 cases of hepatoblastoma, out of which 7 were boys and 4 were girls and male, female ratio was 1.7:1[28].

Jeng Chang Chen et al. studied 55 cases of hepatocellular carcinoma in which 43 were males and 12 were females and male, female ratio was 3.6:1[11].

Yen Hsuan Ni, et al. studied 71 cases of hepatocellular carcinoma in a period of 25

years and male, female ratio was 3.2:1 (M:F 54:17)[30].

Mistry et al. reported two cases of undifferentiated embryonal sarcoma, both cases were male patients[17].

Francois et al. reported 22 cases of benign tumors during 1965 to 1982 at Sainte-Justine Hospital, in which 16 cases were hemangioendothelioma and male, female ratio was 9:13[6].

George et al. reported 16 cases of hemangioendothelioma, in which male, female ratio was 3:5[9].

Lack et al. during a period of 57 years at Children's Hospital, Boston, reported two cases of hepatocellular adenoma and the male, female ratio was 1:1[13].

STAGING OF TUMOR

Gonzalez-Crussi et al. studied 21 cases of hepatoblastoma at Children's Memorial Hospital of Chicago between 1954 and 1981, in which 11 cases were confined to one lobe (Stage I), 7 cases were in both lobes (Stage III) and one case was at stage IV with presence of distant metastasis. Staging was not done in two cases[10].

Ernest et al. studied 54 cases of hepatoblastoma, 28 were confined to right lobe, 7 involved the left lobe only and 18 involved both lobes[4].

Frederic et al. reported 26 cases of hepatoblastoma and 3 cases of hepatocellular carcinoma during a 13 years period from 1973 to 1984. In 26 cases of hepatoblastoma, 15

were confined to right lobe, 8 were confined to left lobe and 3 were bilateral and in the 3 cases of hepatocellular carcinoma, two cases were in right lobe and one case was in left lobe[7].

Gandhi et al. reported 6 cases of hepatoblastoma in which 4 cases were confined to right lobe and two cases were confined to left lobe[8].

Khosla et al. reported 12 cases of hepatoblastoma and two cases of undifferentiated embryonal sarcoma from 1982 to 1987 at All India Institute of Medical Sciences, 8 cases were confined to right lobe, 3 were involved in both lobes, one was involved in left lobe[12].

Madhusudhana Murthy et al. reported 7 cases of hepatoblastoma, in which 5 cases involved both lobes, one in the right lobe and other in the left lobe[15].

Jeng Chang Chen et al. reported 48 cases of hepatocellular carcinoma, in which bilateral involvement was found in 32, left lobe was involved in 9 and right lobe in 7[11].

Wei Jao Chen et al. reported 55 cases of malignant hepatic tumors, in which one was liposarcoma, in 30 cases of histologically proven hepatocellular carcinoma, 23 cases involved both lobes, four were confined to left lobe and three were confined to right lobe and in 10 cases of histologically proven hepatoblastoma, 4 were in both lobes, 4 were in right lobe and 2 were in left lobe[28].

Francois et al. reported 22 cases of benign liver tumors, 16 cases of hemangioendothelioma and 4 cases of mesenchymal hamartoma during 25 years from 1965 to 1989. The hemangioendothelioma cases were 6 on the left lobe, 5 on the right lobe and 5 on both lobes. All the 4 cases of mesenchymal hamartoma, were on the right lobe[6].

George et al. reported 16 cases of hemangioendothelioma during 32 years from 1955 to 1987. All the cases had diffuse disease[9].

Mistry et al. reported 2 cases of undifferentiated embryonal sarcoma, both were confined to right lobe[17].

Lack et al. reported 2 cases of hepatocellular adenoma during 57 years, at Children's Hospital, Boston. Both cases were confined to right lobe[13].

ALPHA FETO PROTEIN

Human AFP is a glycoprotein containing a molecule of biantennary glycan and previous studies have shown that some molecular structural differences in the carbohydrate chain exist according to different sources of AFP synthesis and that such microheterogeneity in carbohydrate moiety can be definitely identified by the reactivity with lectins. Concanavalin A, lens culinaris hemagglutinin and phytohemagglutinin-E are lectins commonly used and based on reactivity to these lectins, AFP from patients with hepatic malignancies, benign liver diseases and germ cell tumors can be clearly classified into three types in adults. Subfractionation of serum alpha feto protein is a useful method to discriminate between yolksac tumors, hepatic malignancies and benign liver diseases in adults but has not been validated in infants and children[31].

Following surgical resection of pediatric liver tumors, a sharp decrease and return to normal serum AFP concentrations within approximately 2 months indicated the completeness of surgical procedure. Importance of the AFP assay in the follow up of post surgical resection of tumor for the assessment of the completeness of surgical procedure, the prognosis, and the early detection of tumor recurrence is stressed[7].

Frederic et al. reported 29 cases of malignant hepatic tumor, in which AFP level range from 340ng/ml to 5,30,000 ng/ml and it was normal in three of cases. All patients cured had normal values of AFP with in approximately 2 months and never demonstrated subsequent changes. In four cases after normal postoperative AFP levels a secondary increase in serum AFP was noted 4 to 14 months later. This corresponded to pulmonary metastases in two cases and local recurrence in two others. Persisting high level after operation was indicative of residual mass in four cases. There are usually no difficulties in diagnosis when the clinical examination and ultrasonogram evidence of an intrahepatic mass together with elevated serum AFP level of 1,000 to 10,000 ng/ml (normal 16ng/ml or less). Normal serum AFP level may be demonstrated in 10% of hepatoblastoma and in 10% of hepatocellular carcinoma. Serum AFP may also be elevated in case of hamartoma but the levels are usually lower than with malignant tumors. Therefore, biopsies may be required if there is doubt concerning the benign or malignant nature of liver tumor, before planning any mode of treatment[7].

Wei Jao Chen et al. reported AFP was elevated in 28 out of 30 hepatocellular carcinoma (93%) and in 8 out of 9 hepatoblastoma children (89%)[28].

Francois et al. reported 22 benign tumours during 1965 to 1989 in which AFP levels were elevated in 3 of 16 infants with hemangioendothelioma and in 1 child among 4 cases of hamartoma. Serum AFP levels were also increased in half of infants who were tested in this series as control. However, this may not be significant because AFP levels are normally elevated during the first few week of life[6].

George Holcomb et al. found that AFP level was elevated in 3 out of 8 patients of

hemangioendothelioma but did not correlate with outcome[9].

Mistry et al. reported two cases of undifferentiated embryonal sarcoma and in both AFP was normal[17].

Klein et al. reported 13 cases of hepatocellular carcinoma and one cholangiocarcinoma in people younger than 30 years. In 13 cases of hepatocellular carcinoma, serum AFP levels was normal in 5 cases, not done in two cases and elevated in remaining 6 cases. The range was from 78,000 to 2,202,600 ng/ml[27].

Khosla et al. reported serum AFP levels was markedly elevated 1000-10,000 times of normal controls in four of the six patients of hepatoblastoma. It was normal in the two patients of undifferentiated embryonal sarcoma[12].

HISTOLOGIC CLASSIFICATION OF HEPATOBLASTOMA

Gonzalez-Crussi et al. reported 21 cases of hepatoblastoma during 27 years from 1954 to 1981 in Children's Memorial Hospital at Chicago, in which 17 (81%) were epithelial type hepatoblastoma, 4 (19%) were mixed (epithelial and mesenchymal). In 17 epithelial type hepatoblastoma, 5 (29.4%) were purely fetal, 4 (23.5%) were fetal predominant, 3 (17.6%) were fetal and embryonal pattern and 5 (29.5%) were macrotrabecular[10].

Lack et al. reported 54 cases of hepatoblastoma during 57 years from 1924 to 1981 (Table: 1)[4].

Table : 1

Histological classification of Hepatoblastoma

♦ Conventional hepatoblastoma	
epithelial (59.25%)	
• embryonal predominant	19
• Fetal predominant	13
Mixed (epithelial and mesenchymal) (22.25%)	12
Indeterminate (9.25%)	5
♦ Anaplastic hepatoblastoma (9.25%)	5
Total	54

Frederic et al. reported 29 cases of malignant hepatic tumor during 13 years from 1973 to 1984, in which 26 were hepatoblastoma and 3 were hepatocellular carcinoma. One of 3 hepatocellular carcinoma was fibrolamellar carcinoma. In 26 cases of hepatoblastoma, 21 cases were reviewed with Kasai's criteria for hepatoblastoma; only one was of pure epithelial type; the others were of mixed type with a predominant fetal component in five cases and mixed fetal and embryonal component in 15 cases[7].

PROGNOSIS

Age of patients and histopathological subtypes could only indicate outcome, while tumor size and serum AFP values were not significantly related to prognosis[10].

Lack et al. reported 49 children with hepatoblastoma of conventional type were separated into two groups those who underwent laparotomy and biopsy and those who

underwent laparotomy with attempt at complete resection. There were no long-term survivors in the first group despite the use of varied adjuvant therapy in nine cases. 13 of 29 children undergoing routine or extended hepatic lobectomy were alive without evidence of disease on an average of 9 years later (range: 16 months-21 years). Among 13 cases tumor was confined to one lobe (10 right, three left) in each case. Five of them received adjuvent therapy. Hepatoblastoma resected from 11 of 13 survivors was epithelial type (85%) with seven having predominantly fetal pattern and two remaining tumors had mixed histology with a preponderance of fetal epithelial elements. None of the children with anaplastic tumors survived. Average duration of disease from diagnosis to death for all children was 8 months (range: 1 month to 27 months): 82% died in the first year[4].

Frederic et al. reported 29 cases of liver malignancies, 26 hepatoblastoma and 3 hepatocellular carcinoma were treated in a 13 years period. All children were submitted to operation but four had nonresectable tumors, even after chemotherapy. Surgery in the 25 cases consisted of right lobectomy in 14, a left lobectomy in 9 and a tumorectomy in 2. Ten children died, one in the immediate post operative period, eight others from the disease and one from a complication of chemotherapy. Follow up for the 18 surviving children, all recurrence and metastasis free with normal AFP is less than 2 years for 4 and from 2 to 11 years for 14[7].

Gandhi et al. reported 6 cases of hepatoblastoma in Seth G.S.Medical College. All have undergone resection. Since hepatoblastoma are resistant to radiotherapy and chemotherapy, the only effective treatment was surgical. In tumors restricted to either right or left lobe, resection of involved lobe is a practical procedure. Results of resection of left

lobe are better than that of resection of right. In this study, 2 children submitted to left hepatic lobectomy have done well and one of them, showed no evidence of local recurrence or distant metastasis 6 years after surgery. Three children were submitted to right hepatic lobectomy. Two of them did well in the initial post operative period and one of them died soon after surgery. One of two, who was doing well post operatively, died of a sudden cardiorespiratory arrest on 5th post operative day and the other succumbed to broncho pneumonia. A wide wedge excision was carried out in one case. This child did well for 1½ years and had no evidence of metastasis. Unfortunately the child was lost for followup. It seems that a limited resection may be justifiable and worth while in a selected case. Madhusudhana murthy et al. reported 7 cases of hepatoblastoma of which there were two survivors after successful resection and another case was showing good response with chemotherapy and was awaiting surgery. Other cases were un resectable bilateral tumor, treated only with chemotherapy and lost to followup[8].

Jeng Chang Chen et al. studied 55 patients with hepatocellular carcinoma, they were divided into three groups: resectable, chemotherapeutic and untreated. The survival data of 10 children with resectable hepatocellular carcinoma, ranged from 1 month to 171 month, 4 patients were dead, 5 patients were alive, and one patient lost to followup[11].

Wei Jao Chen reported 55 cases of primary malignant tumor of liver in infants and children, in which 44 cases were hepatocellular carcinoma, ten cases were hepatoblastoma and one was liposarcoma. He observed 60% resectable rate and 40% survival rate for hepatoblastoma but for hepatocellular carcinoma, the resectability was less than 10%. Only two children were cured of hepatocellular carcinoma. Among those without tumor

resection, all except two children died within one year. No difference in survival time was observed between those who had chemotherapy and those who did not. Early diagnosis and complete excision of tumor remains the only way to long term survival[28].

Yes-Hsuan Ni et al. reported 71 cases of hepatocellular carcinoma from 1964 to 1989 at the National Taiwan University Hospital. Only 10% of the patients survived longer than 1 year after the onset of the initial symptom. Among 49 patients who could be followed, only two had long term survival over five years, both received surgical resection. Observation indicated that the prognosis for children with symptomatic hepatocellular carcinoma is grave, but surgical resection whenever possible, should be carried out[30].

Francois et al. reported 22 cases of benign liver tumors between 1965 and 1989. At mean follow up of 38 months, 21 of 22 patients were cured or were asymptomatic. The 96% survival in this series of benign liver tumors contrasts with high mortality rates (90%) reported in the literature and illustrates the spectacular improvements that have been made in the diagnosis and management[6].

George et al. reported 16 cases of hemangioendothelioma from 1955 to 1987 in Children's Hospital of Philadelphia. The survival rate in this series was 80%. Highest survival in this study was 28 years after diagnosis[9].

Mistry et al. reported two cases of undifferentiated embryonal sarcoma, in which one was alive four years after surgery and one died 16 months after hepatic resection[17].

AIM OF THE STUDY

- To study incidence of pediatric liver tumor in Institute of Child Health, Chennai during period of 1999 to 2004.

- To study clinical behaviour and response of tumor to various mode of treatment.

- To study alpha feto protein correlation of various liver tumors.

- To study histopathological features of pediatric liver tumors.

MATERIALS AND METHODS

The tumor board records and medical records of each patients treated for pediatric liver tumors at Institute of Child Health in Chennai from 1999 to 2004 were retrospectively reviewed. Details regarding the surgery, clinical features, chemotherapy and follow up were collected.

A total number of 39 cases of pediatric liver tumors were taken into study, out of which 20 cases were resected specimens and 19 cases were small biopsies.

The specimen had been fixed in 10% neutral buffered formalin immediately after removal. The following aspects of gross examination had been under taken.

1. Weight of specimen
2. External surface of tumors
3. Multiple sections of specimen had been made
4. Measurement of tumor was taken.
5. Sections were taken from the tumor, tumor liver interface and from adjacent normal liver.

The bits were routinely processed. The sections were cut and stained with hematoxylin and eosin staining.

The histological features were studied under light microscope. Other details like age, sex, onset, duration, size and site were noted. Clinico pathological correlation was done.

RESULTS AND OBSERVATION

This is a histopathological study of 39 cases of pediatric liver tumor in the Department of Pathology, ICH and HC, Chennai the period from 1999 to 2004.

In 39 cases of pediatric liver tumors in our study 19 were small biopsies. In remaining 20 cases, right lobectomy done in 12 cases, left lobectomy done in 6 cases, enucleation done in one case and segmentectomy done in one case.

Table : 2

Histological subtype	No. of cases
Hepatoblastoma	28
Hemangioendothelioma	6
Hepatocellular carcinoma	2
Undifferentiated embryonal sarcoma	2
Hepatocellular adenoma	1
Total	**39**

In our study age range for hepatoblastoma was 4 month to 6 year in 28 out of 39 cases of pediatric liver tumor, and accounted for 53.5% with peak incidence between the age group of 2 months to 24 months.

Table: 3

HEPATOBLASTOMA

Age in years	SEX	Total No. of Cases

	Male	Female	
0-1	6	10	16
1-2	2	3	5
2-3	4	1	5
3-4	-	1	1
>5	1	-	1
Total	**13**	**15**	**28**

Table: 4

HEMANGIOENDOTHELIOMA

Age	**SEX**		**Total No. of Cases**
	Male	**Female**	
0-1 month	-	1	1
1 month - 1 year	-	2	2
1-2 years	-	-	-
2-3 years	1	1	2
>3 years	-	1	1
Total	**1**	**5**	**6**

Table: 5

HEPATOCELLULAR CARCINOMA

Age	SEX		Location of tumor
	Male	Female	
0-5 Years	-	-	-
5-10 years	2	-	Right side
Total	**2**	**-**	**2**

Table: 6

UNDIFFERENTIATED EMBRYONAL SARCOMA

Age	SEX		Location of tumor
	Male	Female	
0-5 Years	-	-	-
5-10 years	2	-	Right side
Total	**2**	**-**	**2**

Table: 7

HEPATOBLASTOMA

Right side	14 cases
Left side	6 cases
Both side	8 cases

Table: 8

HEMANGIOENDOTHELIOMA

Right side	3 cases
Left side	1 case
Both side	2 cases

Only one case of hepatocellular adenoma reported at 6 years in male patient in right lobe.

ALPHA FETO PROTEIN LEVEL

- In our study 22 cases of hepato blastoma showed serum AFP level range from 280 to 60,000 ng/ml. They were about 20-4285 times of normal. Serum AFP level was not done in 6 cases of hepatoblastoma.

- In one case of hemangioendothelioma showed 79 times of normal serum AFP (1108 ng/ml), not done in two cases and normal level in 3 cases.

- In both cases of hepatocellular carcinoma, serum AFP level was elevated, around 2140 times of normal.

- Serum AFP level was normal in one case of hepatocellular adenoma and in two cases of undifferentiated embryonal sarcoma.

HISTOLOGICAL CLASSIFICATION OF HEPATOBLASTOMA

Table: 9

Epithelial	
Purely fetal	12
Fetal and embryonal	12
Anaplastic	-
Small cell	-
Macrotrabecular	1
Epithelial and mesenchymal	**3**
Total	**28**

PROGNOSIS

In our study out of 39 cases, follow up study was available only in 6 cases of hepatoblastoma and in each one case of hemangioendothelioma, hepatocellular carcinoma and undifferentiated embryonal sarcoma.

Maximum 3 year followup without tumor recurrence was available in two cases of hepatoblastoma. In both cases complete excision of tumor and adjuvant chemotherapy in the form of preoperative in one case and post operative chemotherapy in other case. Both cases were epithelial hepatoblastoma, in which one was purely fetal and other was combined fetal and embryonal and both cases were confined to left lobe.

In all 6 cases of hepatoblastoma with longer survival more than one year, all were stage I tumor (resectable and limited to one lobe and complete excision of tumor was done in all 6 cases).

2 year follow up without any recurrence in one case of hepatocellular carcinoma was available, in that case preoperative chemotherapy, followed by complete excision of tumor was done.

1 year follow up without any recurrence in one case of undifferentiated embryonal sarcoma was seen. In that case complete excision and post operative chemotherapy given.

Only with medical treatment with out any surgical treatment, 3 year survival rate was seen in one case of hemangioendothelioma.

DISCUSSION

WHO CLASSIFICATION OF PRIMARY LIVER TUMORS AND TUMOR LIKE LESIONS

Epithelial tumors or tumor like lesions

Benign

Large regenerative nodule

Lowgrade dysplastic nodule

Highgrade dysplastic nodule

Hepatocellular adenoma

Focal nodular hyperplasia

Bile duct adenoma

Bile duct hamartoma

Biliary cystadenoma

Intraductal biliary papillomatosis

Congenital biliary cyst

Focal fatty change

Malignant

- Hepatocellular carcinoma including fibrolamellar variant
- Combined hepatocellular and cholangio carcinoma
- Cholangiocarcinoma-peripheral, hilar and extra hepatic type
- Biliary cystadeno carcinoma
- Hepatoblastoma

- Intraductal papillary adenocarcinoma

Non-epithelial tumors or tumor like lesions

Benign

- Hemangioma
- Angiomyolipoma
- Infantile hemangioendothelioma
- Mesenchymal hamartoma
- Localized fibrous tumor
- Solitary necrotic nodule
- Inflammatory pseudotumor
- Infectious cyst
- Other rare benign tumors

Malignant

- Epithelial hemangioendothelioma
- Angiosarcoma
- Undifferentiated embryonal sarcoma
- Lymphoma and other hematopoietic tumors
- Kaposi's sarcoma
- Other malignant tumors

CLASSIFICATION OF HEPATIC TUMORS IN CHILDREN

Benign tumors and pseudo tumors

- **Hepatocellular**

- Focal nodular hyperplasia
    - Nodular regenerative hyperplasia
    - Hepatocellular adenoma
- **Mesodermal**
    - Infantile hemangioendothelioma
    - Mesenchymal hamartoma

Malignant neoplasms

- **Hepatocellular**
    - Hepatoblastoma
    - Hepatocellular carcinoma
- **Mesodermal**
    - Undifferentiated embryonal sarcoma
    - Angiosarcoma
    - Embryonal rhabdomyosarcoma of the biliary tract

STAGING OF HEPATOBLASTOMA

Stage I : Complete resection

Stage II : Microscopic residual tumor

- Intra hepatic
- Extra hepatic

Stage III : Gross residual tumor

- Primary completely resected, nodes positive and/or tumor spill.

- Primary not completely resected, nodes positive and/or tumor spill.

Stage IV : Metastatic disease

- Primary completely resected
- Primary not completely resected

STAGING OF HEPATOBLASTOMA BY CHILDREN'S CANCER STUDY GROUP

Stage I : Localised tumor that was completely resected as primary treatment

Stage II : Localised residual tumor following incomplete resection

Stage III : Tumor present in both lobes

Stage IV : Presence of distant metastases regardless of the extent of liver involvement.

HISTOLOGICAL CLASSIFICATION OF HEPATOBLASTOMA

I - Epithelial type

A. Fetal pattern

B. Embryonal and fetal pattern

C. Macrotrabecular pattern

D. Small cell undifferentiated pattern

II - Mixed epithelial and mesenchymal type

A. Without teratoid features

B. With teratoid features

GROSS

In our study the average diameter of hepatoblastoma was 8cm (range: 3-14cm). The weight of surgically resected specimens ranged from 300 to 1400 gm. Externally, most hepatoblastoma were coarsely nodular with prominent vascularity and intact overlying Glisson's capsule. On cross section most of the hepatoblastoma were typically variegated and has bulging lobules of varying size, colour and consistency (Fig. 1). Tumors were often sharply delimited from adjacent liver parenchyma, occasionally giving a spurious impression of encapsulation (Fig. 1).

- In our study, one case of hemangioendothelioma in 12 days female child, in which the tumor presented as capsulated exophytic mass from anterioinferior aspect of left lobe of liver and cut section of tumor was solid and hemorrhagic.

- In one case of hepatocellular carcinoma, tumor presented as multiple nodules throughout the liver, ranging from 3mm-3cm in the background of cirrhosis.

- Hepatocellular adenoma in our study presented as pedunculated mass measuring as 6cm from inferior aspect of right lobe (Fig. 11).

- In our study, one case of undifferentiated embryonal sarcoma presented as solid greywhite nodule protruding into larger space of adjacent spongy areas filled with greenish material and blood in some spaces (Fig. 13).

MICROSCOPIC FEATURES

In our study, hepatoblastoma with predominant fetal pattern in which neoplastic liver cells were typically arranged in cords or plates from two to three cells thick or had a sheet like configuration (Fig. 3). Extra medullary hematopoiesis was noted in fetal area in predominant cases of hepatoblastoma (Fig. 2). An acinar or pseudo glandular pattern was noted in embryonal areas (Fig. 4).

Osteoid was noted in all 3 cases of mixed hepatoblastoma (Fig. 6), immature spindle cells noted in one case and calcification in other case, in our study.

In hemangioendothelioma, the lesion was composed of vascular channels lined by a single continuous layer of plump endothelial cells in a supporting fibrous stroma. The area was well separated from normal liver parenchyma (Fig. 8).

Hepatocellular carcinoma arised in the background of cirrhosis in one case of our

study (Fig. 9).

Hepatocellular adenoma composed of sheets of tumor cells in trabeculae, two cells thick separated by compressed sinusoids and there were no fibrous septa or portal tracts within tumor tissue. The tumor cells were the same size or slightly larger than the normal hepatocytes (Fig. 12).

Undifferentiated embryonal sarcoma composed of a mixture of spindled and stellate cells in a myxoid stroma. The tumor cells have bubbly light pink cytoplasm (Fig. 14 and 15).

Cytologic criteria to subtype hepatoblastoma by Ishak and Glunz

Fetal cell - tumor predominantly or exclusively composed of cells of obvious hepatocytic nature but smaller than hepatocytes of uninvolved liver away from sites of compression. N/C ratio of fetal cells is 1/2 to 1/4 (compared to 1/4 to 1/6 in normal liver cells), named as fetal cell, because these cells resemble hepatocytes of fetus after establishment of the hematopoietic function at 6-8 weeks of gestation[10].

Embryonal cell - cells of possible hepatocytic nature but with N/C ratio of 1/1 or 1/2 morphology and histologic arrangement of embryonal cells are reminiscent of the liver of embryos before 6th week of gestation[10].

In mixed hepatoblastoma (mesenchymal and epithelial cell); mesenchymal component was loosely defined as any mesenchymal tissue, other than blood vessels, mature supporting stroma or hematopoietic tissue, that appeared to be an integral part of tumor[10].

Anaplasia defined by Beckwith and Palmer, as cells containing hyperchromatic nuclei from 3 to 5 times the size of neighbouring nuclei, hyperchromatic and bizarre atypical mitoses with obvious polyploidy[10].

Predominant pattern is listed, the histologic appearance that occupied approximately 2/3 or more of the area of tumor represented on the slides. If additional pattern were present, but made up less than 1/3 of surface examined, there were listed as other components, if more than 1/3 they were listed in combination with the predominant pattern[10].

Primary hepatic tumors are third largest group of solid abdominal neoplasms in children next to neuroblastoma and Wilms' tumor[28].

50 to 60% of primary liver tumors in children are malignant, in which hepatoblastoma is most common followed by hepato cellular carcinoma. Undifferentiated embryonal sarcoma is a rare malignant tumor. Among benign tumors, vascular tumors-hemangioendothelioma is most common followed by mesenchymal hamartoma. Hepato cellular adenoma is a rare benign tumur in children[13].

In our study out of 39 cases of pediatric liver tumor from 1999 to 2004 at ICH & HC in Chennai and it was compared to AFIP studies (Table 10).

Table: 10

Comparison of incidence of liver tumors between AFIP[23] and our study

	Number		Percentage (%)	
	Our Study 1999-04	**AFIP 1970-99**	**Our Study**	**AFIP**
Hepatoblastoma	28	198	71.80	27.6
Hepatocellular carcinoma	2	135	5.13	18.9
Infantile hemangioendothelioma	6	119	15.38	16.5
Focal nodular hyperplasia	-	72	-	10.1
Mesenchymal hamartoma	-	57	-	8.0
Undifferentiated embryonal sarcoma	2	52	5.13	7.2
Nodular regenerative hyperplasia	-	32	-	4.5
Hepatocellular adenoma	1	27	2.56	3.8
Angiosarcoma	-	17	-	2.4
Embryonal rhabdomyosarcoma	-	7	-	1.0
Total	**39**	**716**	**100%**	**100%**

Table: 11

Age distribution of hepatoblastoma in 28 cases in our studies

	Age Range	No	Percentage (%)
In Our Study	0 - 1 year	15	53.5%
	1 - 2 year	6	21.5%
	2 - 3 year	5	17.8%
	3 - 4 year	1	3.6%
	> 4 year	1	3.6%
Total		**28**	**100%**

Table: 12

Age distribution of hepatoblastoma in 105 cases from 1970 to 1989 at AFIP[23]

Age Range	No	Percentage %
0 - 1 year	36	34.28
1 - 2 year	42	40.00
3 - 5 year	13	12.38
6 - 10 year	8	7.62
11 - 15 year	3	2.86
16 - 20 year	3	2.86
Total	**105**	**100%**

Age range in our studies was 4 months to 6 years, average age at presentation was 19 month.

Lack et al., reported 54 cases of hepatoblastoma in which age range was between 4 months to 4½ years, average age at presentation was 17 month[4].

Gonzalez Crussi et al. reported 21 cases of hepatoblastoma in which age range was

37 hours to 12 years but 17 cases were less than two years. In our study, 21 out of 28 cases were less than 2 years[10].

Table: 13

Age distribution of hemangioendothelioma in 6 cases

Age group	Total no. of cases	Percentage
0 - 1 month	1 case	16.66%
1 month - 1 year	2 case	33.34%
1 - 2 years	-	-
2 - 3 years	2 case	33.34%
3 - 4 years	1 case	16.66%
> 4 years	6 case	100%

Table: 14

Age distribution of hemangioendothelioma in 102 cases from 1970 - 1989 at AFIP[23]

Age group	Total no. of cases	Percentage
0 - 1 month	35 case	34.32%
1 - 6 years	55 case	53.92%
7 - 12 years	6 case	5.88%
>1 year	6 case	5.88%
> 4 years	102 case	100%

In our study age range of hemangioendothelioma was 12 days to 39 month, average age at presentation was 18 month.

Francois Linkes et al., reported 16 cases of hemangioendothelioma in which age range was birth to 14 years and mean age at presentation was 2.3 years[6].

George et al., reported 16 cases of hemangioendothelioma in which age range was 2 days to 14 years and mean age at presentation was 7 month[9].

UNDIFFERENTIATED EMBRYONAL SARCOMA (Malignant mesenchymoma)

In our study two cases of undifferentiated embryonal sarcoma reported, age at presentation was 8 years in one and 9 years in other case.

Mistry et al., reported two cases of undifferentiated embryonal sarcoma, both were 9 years old at presentation[17].

HEPATO CELLULAR CARCINOMA

Two cases of hepato cellular carcinoma in our study, age presentation in one case was 9 years and 10 years in other.

Yen Hsuan Ni. studied 55 cases of hepatocellular carcinoma between 1964 to 1989 age range was 3 to 17 years, mean age was 9.7 years[30].

One case of hepato cellular adenoma at 6 years reported in our study.

SEX DISTRIBUTION

In our study male female ratio was 1:1.1 for 28 cases of hepatoblastoma.

Gonzelez - Crussi et al., reported 21 cases of hepatoblastoma, in which male, female ratio was 1.6:1[10].

6 cases of hemangioendothelioma in our study during 6 years, in which male,

female ratio was 1:5.

George et al., reported male, female ratio was 3:5 and Francois et al., reported male, female ratio was 1:1.5 for hemangioendothelioma[9].

Two cases of hepato cellular carcinoma, two cases of un differentiated embryonal sarcoma and one case of hepatocellular adenoma in our study was reported only in male.

Mistry et al., reported two cases of undifferentiated embryonal sarcoma and both cases were reported in male patients[17].

Jeng Chang Chen et al., studied 55 cases of hepatocellular carcinoma in which the male, female ratio of 3.5:1[11].

LOCATION OF TUMORS

Of the 28 cases of hepatoblastoma in our study, 14 were confined to right lobe, 6 were in left lobe and 8 cases involved both lobes.

Ernest et al., reported 54 cases of hepatoblastoma, 28 were confined to right lobe, 7 were in left lobe and 18 involved both lobes[4].

6 cases of hemangioendothelioma in our study, 2 were in right lobe, two were in left lobe and two were in both lobes.

Francois et al., reported 16 cases of hemangioendothelioma in which 6 were in Lt lobe, 5 were in Rt lobe and 5 were in both lobes[6].

In our study one case of hepatocellular carcinoma was in right lobe and other was in

both lobes.

Jeng Chang Chen et al., reported 48 cases of hepato cellular carcinoma in which bilateral involvement was found in 32, left lobe was involved in 9 and right lobe in seven[11].

Both cases of undifferentiated embryonal sarcoma in our study was confined to right lobe.

Mistry et al., reported two cases of undifferentiated embryonal sarcoma and both were confined to right lobe like our study[17].

One case of hepatocellular adenoma in our study was confined to right lobe.

ALPHA FETO PROTEIN

Alpha feto protein level was increased in 22 cases of hepatoblastoma with range from 20 to 4285 times of normal in our study. Serum AFP was increased in both cases of hepatocellular carcinoma and in one case of hemangioendothelioma.

Serum AFP level was normal in both cases of undifferentiated embryonal carcinoma and in hepatocellular adenoma in our study.

Wei Jao Chen et al., reported serum AFP was elevated in 28 out of 30 HCC (93%) and in eight out of 9 hepatoblastoma children[28].

Francois et al., reported 22 benign tumors during 1965 to 1989 in which AFP levels were elevated in 3 to 16 infants with hemangioendothelioma[6].

PROGNOSIS

Main mode of treatment for pediatric malignant liver tumor was resection of tumor. In unresectable tumors and in large tumors, pre operative chemo therapy was given, followed by surgical resection. Post operative chemo therapy reduces incidence of recurrence after surgical resection.

In our study, follow up study was available only in 9 cases of pediatric liver tumor, in which one was hemangioendothelioma, remaining were malignant pediatric liver tumors.

In all eight malignant pediatric liver tumors, complete resection of tumors was done and adjuvant therapy in the form of pre operative chemotherapy in some cases and post operative chemotherapy in some cases.

Yen Hsuan Ni et al., reported 71 cases of hepatocellular carcinoma, in which he observed only two long term survivors among 49 patients who could be followed more than 5 years, both received surgical resection. So he quoted prognosis for children with symptomatic hepato cellular carcinoma is grave but surgical resection when ever possible should be carried out[30].

Wei Jaco Chen et al., reported 55 cases of primary malignant tumor of liver in infants and children, he observed 60% resectable rate and 40% survival rate for hepatoblastoma but for hepato cellular carcinoma, the resectability was less than 10%. He observed no difference in survival time between those who had chemotherapy and those who did not. Early diagnosis and complete excision of tumor remains the only way to long

term survival[28].

Mistry et al., reported two cases of undifferentiated embryonal sarcoma in which one was alive four year after surgery and one died 16 months after surgical resection[17].

SUMMARY

Total number of cases of pediatric liver tumors studied during the period of study 1999 - 2004 in department of Pathology ICH and HC Chennai were 39.

This study has helped us to make following inferences.

1. Hepatoblastoma was the most common pediatric liver tumors accounting for 71.80%.

2. Following hepatoblastoma hemangioendothelioma was second most common pediatric liver tumors accounting for 15.38%.

3. Among malignant pediatric liver tumors, next to hepatoblastoma, hepatocellular carcinoma and undifferentiated embryonal sarcoma were each accounting for 5.13% in our study.

4. None of tumor like condition like mesenchymal hamartoma and focal nodular hyperplasia was reported during our study period.

5. Only one case of hepatocellular adenoma was reported during this period.

6. Peak incidence of hepatoblastoma was between birth to one year (57%).

7. Only one hepatoblastoma was reported above 5 years.

8. 2 cases of hepatocellular carcinoma and 2 cases of undifferentiated

embryonal sarcoma in this study was reported above 5 years.

9. In our study male, female ratio for 28 cases of hepatoblastoma was 1:1.1, in contrast to male preponderance in literature.

10. Male female ratio for hemangioendothelioma was 1:5 like female preponderance in literature.

11. In our study pediatric hepatic tumor including benign and malignant tumors most commonly involved right lobe of liver.

12. Serum AFP level was increased in hepatoblastoma and in hepatocellular carcinoma, normal in hepato cellular adenoma and in undifferentiated embryonal sarcoma. Serum AFP level was increased in few cases of hemangioendothelioma.

13. In hepatoblastoma, most common histological subtype was epithelial type composed of fetal and embryonal cell, and epithelial type predominantly fetal cells, each in 12 cases.

14. Main mode of treatment for pediatric malignant hepatic tumour was surgical resection whenever possible and pre-operative chemotherapy for large tumors to reduce size before surgery and also for unresetable tumors. Post operative chemo therapy is used to reduce incidence of recurrence.

CONCLUSION

There has been a substantial improvement in survival in patients with pediatric liver tumors over 30 years. Through better understanding of pathological diagnosis, refined surgical staging, newer and more effective radiological techniques and standardized multimodal therapies, a substantial number of children diagnosed with this highly malignant tumor can expect to survive their disease.

96% survival in benign liver tumors nowadays contrast with high mortality rates (90%) reported in the older literature. It illustrates the specular improvements that have been made in diagnosis and management.

Nowadays most of hemangioendothelioma treated only with medical treatment, proposed longer survival, because more effective management of congestive cardiac failure.

Despite the remarkable success in the treatment of pediatric liver tumors, there is a still remarkable percentage of patients who will suffer a relapse, because of surgical complication of liver tumors, difficulties in surgical approach to complete resection of tumors and decreased effectiveness of chemotherapy when compared to chemotherapeutic agent of Wilms' tumor. It is challenge and goal of surgical pathologists, pediatric surgeons, radiologists and oncologists treating children with liver tumors to improve even more the incredible achievement. These challenges to improve the survival of patients with liver tumors will be achieved by their continued, collaborative efforts of all the medical disciplines involved in the treatment of pediatric liver tumors.

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